UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,557	12/22/2003	Khalid K. Sadozai	0103343.00128US1	5063

23483 7590 01/25/2010

WILMERHALE/BOSTON
60 STATE STREET
BOSTON, MA 02109

EXAMINER	
BROWN, COURTNEY A	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
01/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

michael.mathewson@wilmerhale.com
teresa.carvalho@wilmerhale.com
sharon.matthews@wilmerhale.com

Office Action Summary	Application No.	Applicant(s)	
	10/743,557	SADOZAI ET AL.	
	Examiner	Art Unit	
	COURTNEY BROWN	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-16 and 18-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-16 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt/Status of Claims

This Office Action is in response to the amendment filed October 8,2009. Claims 11-16 and 18-22 are pending in the application. Claims 1-10, 17 and 23-48 have been cancelled. Claims 111,14-16 and 20 have been amended. Claims 11-16 and 18-22 are being examined for patentability.

As stated in the interview on October 9, 2009, the new limitation, 'single hydrated particle' phase required a new search. In view of the new search, the Examiner has found this art which has been discussed below.

Rejections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Withdrawn Objection(s)

The objection of claim 20 has been **withdrawn.**

New Rejection(s) Necessitated by the Amendment filed on October 8, 2009

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-16 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leshchiner et al. (US Patent 5,143,724) in combination with Fujita et al. (JP 2000230001 A) in view of Chasin et al. (US Patent 5,942,241), Aeschlimann et al. (US Patent 7196180) and Calias et al. (US Patent 6521223 B1).

Applicant's Invention

Applicant claims a method of augmenting tissue in a subject that is in need of tissue augmentation, the method comprising: a) inserting a needle into a subject at a location in the subject that is in need of tissue augmentation, wherein the needle is coupled to a syringe loaded with a cross linked HA (i.e., hyaluronic) composition that includes cross linked, water-insoluble, hydrated HA gel particles, wherein the HA includes crosslinks represented by the following structural formula: HA'--U--R2--U--HA' wherein: each HA' is the same or different cross linked HA' molecule; each U is independently an optionally substituted O-acyl isourea or N-acyl urea; and R2 is optionally substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl aryl, heteroaryl, heterocyclyl, cycloaliphaticalkyl, aralkyl, heteroaralkyl, or heterocyclylalkyl, wherein the HA gel particles have an average particle diameter distribution selected from the group consisting of a hydrated particle average diameter between about 20 gm and about 1000 gm, and a dehydrated particle average diameter between about 10 gm and about 500 gm; and wherein the cross linked HA composition

is a single hydrated particle phase; and b) applying force to the syringe, whereby at least a portion of the cross linked HA composition is delivered into the subject.

Determination of the scope and the content of the prior art (MPEP 2141.01)

Leshchiner et al. teach the application of biocompatible viscoelastic gel slurries comprising swollen polymeric gel particles uniformly distributed in a second phase (column 2, lines 59-65) for soft tissue augmentation wherein the basic properties of the mixed gel slurries including: biocompatibility; controlled viscoelasticity and diffusion characteristics; easily controlled residence time at the site of implantation; and easy handling of the material allows its injection through a small diameter needle (column 9, lines 10-22). Leschiner et al. teach the use of a variety of polymeric gels such as hyaluronan (i.e., hyaluronic acid and its biologically acceptable salts)for use in the aforementioned slurries (column 2, line 66 bridging to column 3, lines 1-5) wherein said polymeric gels can be made of polymers which have been insolubilized by cross linking (column 3, lines 23-35). Leshchiner et al. teach that said viscoelastic gel mixtures may contain many other components such as various physiologically active substances, including drugs (column7, lines 60-end). In Examples 1-4, Leshchiner et al. teach that the rheological properties of the aforementioned visoelastic gel mixtures were evaluated with the Bohlin Rheometer System which is a computerized rheometer with controlled shear rate and which can operate in three modes: viscometry, oscillation and relaxation wherein measurements of viscoelastic

properties at various frequencies characterize the balance between elastic (storage modulus G') and viscous (loss modulus G") properties (column 9, lines 32-end). In light of the fact that Leshchiner et al. teach the use of the Bohlin Rheometer System to measure the storage modulus G' and the other viscoelastic properties, it is the Examiner's position that the storage modulus G' and the kinematic viscosity of the instant composition can only be determined experimentally (claims 20-22 of the instant application).

Fujita et al. teach a medical material with an especially high biocompatibity which is produced by incorporating a gel formed from hyaluronic acid. Fujita et al. teach that said gel is crushed with a suitable crusher to an average particle size of 10 mm or smaller (preferably 10-5000 micrometers, see [0019]) and used for injection and then suspended in a concentration of 0.1-5 wt.% in an arbitrary solution, giving a gel slurry suitable for in-vivo decomposable medical materials and cosmetics (abstract).

In reference to claim 18, wherein the instant invention requires that the a multimodial distribution, the specification discloses, on page 13, lines 3-7, that "**the resulting composition has an average diameter distribution that is different from the ground particles before sizing, for example, the average diameter distribution can be a multimodal average diameter distribution, e.g., a bimodal average diameter distribution when two average diameter fractions are selected for the composition. The properties of the multimodal composition are built from the properties of the individual average diameter fractions and their amounts in the composition.**" Therefore, it is the Examiner's position that if the instant composition

has multiple average diameter fractions, it is taught by Fujita et al. Further, the U.S. Patent Office is not equipped with analytical instruments to test prior art compositions for the infinite number of ways that a subsequent applicant may present previously unmeasured characteristics. When as here, the prior art appears to contain the exact same ingredients and applicant's own disclosure supports the suitability of the prior art composition as the inventive composition component, the burden is properly shifted to applicant to show otherwise.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The difference between the invention of the instant application and that of Fujita et al. and Leshchiner et al. is that Fujita et al. and Leshchiner et al. do not expressly teach the use of lidocaine HCL as an anesthetic. This deficiency in Fujita et al. and Leshchiner et al. is cured by the teachings of Chasin et al. Chasin et al. teach the use of a local anesthetic such as lidocaine (see claim 8 of reference) that can be formulated in injectable microspheres in combination with at least one augmenting agent (column 10, lines 20-24). Chasin et al. also teach the use of hyaluronic acid as a preferred controlled release material (column 12, lines 43-56).

The difference between the invention of the instant application and that of Fujita et al. and Leshchiner et al. is that Fujita et al. and Leshchiner et al. do not expressly teach a hyaluronic acid (HA) composition that is cross-linked with different compounds such an optionally substituted o-acyl isourea or N- acyl urea. This deficiency in Fujita et

al. and Leshchiner et al. is cured by the teachings of Aeschlimann et al. Aeschlimann et al. teach introducing a functionalized side chain onto HA wherein the direct carbodiimide-mediated coupling of amines to the carboxyl group of HA in an aqueous environment, with EDC (1-ethyl-3-[3-dimethylaminopropyl] carbodimide), produces O-acyl isourea which is formed as a reactive intermediate that rearranges rapidly to a stable N-acyl urea (see column 12, line 48 bridging to column 13, lines 1-5).

The difference between the invention of the instant application and that of Fujita et al. and Leshchiner et al. is that Fujita et al. and Leshchiner et al. do not expressly teach a cross linked hyaluronic acid (HA) composition that is a single hydrated phase. This deficiency in Fujita et al. and Leshchiner et al. is cured by the teachings of Calias et al. Calias et al. teach single phase gels for preventing the formation of surgical adhesions The gels are prepared by reacting an aqueous solution of a polyanionic polysaccharide, such as hyaluronic acid or carboxymethyl cellulose, with divinyl sulfone, to form a gel, the solution is neutralized, and **a solid is precipitated from the solution (i.e., hydrated particle of instant application)**. The solid can be redissolved in water to form a gel having properties which can be modified to suit a particular application (abstract).

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Fujita et al., Leshchiner et al. and Chasin et al. to arrive at a method of augmenting tissue in a human comprising the use of a cross-linked hyaluronic acid (HA) composition that is cross-linked with different compounds such an optionally substituted o-acyl isourea or N- acyl urea. One skilled in the art at the time the invention was made would have been motivated to use hyaluronic acid (HA) composition that is cross-linked with different compounds such an optionally substituted o-acyl isourea or N- acyl urea because each of the aforementioned references teach hyaluronic acid compositions useful in a method of augmenting tissue. Thus, in view of *In re Kerkhoven, 205 USPQ 1069 (C.C.P.A. 1980)*, it is *prima facie* obvious to combine two or more compositions each of which is taught by prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art, thus claims that requires no more than mixing together two or three conventional hyaluronic acid compositions used for tissue augmentation set forth prima facie obvious subject matter.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Fujita et al., Leshchiner et al. and Aeschlimann et al. to arrive at a method of augmenting tissue in a human comprising the use of a cross-linked hyaluronic acid (HA) composition and lidocaine HCL as an anesthetic. One skilled in the art at the time the invention was made would have been motivated to

use lidocaine HCL as an anesthetic because each of the aforementioned references teach hyaluronic acid compositions useful in a method of augmenting tissue. Thus, in view of *In re Kerkhoven, 205 USPQ 1069 (C.C.P.A. 1980)*, it is *prima facie* obvious to combine two or more compositions each of which is taught by prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art, thus claims that requires no more than mixing together two or three conventional hyaluronic acid compositions used for tissue augmentation set forth prima facie obvious subject matter.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Fujita et al., Leshchiner et al. and Calias et al. to use a cross linked hyaluronic acid (HA) composition that is a single hydrated phase in a method of augmenting tissue. One skilled in the art would have been motivated to use a cross linked hyaluronic acid (HA) composition that is a single hydrated phase Calias et al. teach that two phase gel slurries do suffer from certain drawbacks. For instance, Calias et al. teach that the material must be processed correctly in order to improve the handling properties of the material, and to permit its therapeutic application through the narrow openings of needles and other applicators, particularly for minimally invasive surgical indications. Such processing requires the use of processing equipment and the application of shear forces to the material, which in turn can result in a decrease in viscosity (thinning). Calias et al. teach that two phase materials contain dispersed, heterogeneous particles which tend to plug the narrow

openings of such delivery systems and that a single phase, homogeneous composition is more useful in minimally invasive surgical applications where devices are introduced into the body through narrow access ports. Therefore, Calias et al. teach that it would be highly desirable to formulate a single phase gel solution which is capable of preventing the formation of adhesions, and which can be easily handled and stored for future use, and which possesses the advantageous characteristics of two phase gels (column 2, line 61 bridging to column 3, lines 1-12). Therefore, given the state of the art as evidenced by the teachings of the cited references, and absent any evidence to the contrary, there would have been a reasonable expectation of success in combining the teachings of the cited references to use a HA composition that is single hydrated particle phase in a method of augmenting tissue.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Examiner's Response to Applicant's Remarks

Applicant's arguments filed on October 8, 2009, with respect to the objection of claim 20 have been fully considered but they are moot in view of Applicant's amendment.

Applicant's arguments, filed November 4, 2008, with respect to the 103 rejection of claims 11-16 and 18-22 as being unpatentable over Leshchiner et al. (US Patent 5,143,724) in combination with Fujita et al. (JP 2000230001 A) in view of Chasin et al. (US Patent 5,942,241) and Aeschlimann et al. (US Patent 7196180) have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

The claims remain rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Courtney A. Brown whose telephone number is 571-270-3284. The examiner can normally be reached on 9:00 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Courtney A. Brown
Patent Examiner
Technology Center1600
Group Art Unit 1616

/Ernst V Arnold/
Primary Examiner, Art Unit 1616